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# Neuropathologic Effects of Phenylmethylsulfonyl Fluoride (PMSF)-Induced Promotion and Protection in Organophosphorus Ester-Induced Delayed Neuropathy (OPIDN) in Hens

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***Abstract:*** *The serine/cysteine protease inhibitor phenylmethylsulfonyl fluoride (PMSF) has been used both to promote and to protect against neuropathic events of organophosphorus-induced delayed neuropathy (OPIDN) in hens (Veronesi and Padilla, 1985; Pope and Padilla, 1990; Lotti et al., 1991; Pope et al., 1993; Randall et al., 1997). This study is the first to expand upon this work by using high resolution microscopy provided by epoxy resin embedding and thin sectioning to evaluate neuropathological manifestations of promotion and protection, and to correlate them with associated clinical modifications. To evaluate dose-related effects of OPIDN, single phenyl saligenin phosphate (PSP) dosages of 0.5, 1.0, or 2.5 mg/kg were administered to adult hens. PMSF (90 mg/kg) was given either 4 hours after (for promotion) or 12 hours prior to (for protection) PSP administration. Clinical signs and pathologic changes in the biventer cervicis nerve, which is uniquely sensitive to OPIDN (El-Fawal et al., 1988), were monitored. PSP alone, 2.5 mg/kg, caused severe OPIDN (terminal clinical score 7.5 ± 1.0 [0-8 scale]; neuropathology score 2.7 ± 0.3 [0-4 scale, based on myelinated fiber degeneration]). PMSF given 12 hours prior to PSP gave complete protection (clinical and neuropathology scores of 0; $p<0.0001$ compared to PSP alone). Signs and lesions of OPIDN were absent following 0.5 mg/kg PSP alone, but PMSF given 4 hours after PSP potentiated its neurotoxic effects (all hens had clinical scores of 4.0 and the average neuropathology score was 3.5 ± 0.3; $p<0.0001$ compared to PSP alone). Although quantitative differences were noted, qualitative differences among nerves from hens with OPIDN were not evident, either with light or electron microscopy. At the time of sacrifice, there was a statistically linear relationship ($r^2 = 0.76$) between the clinical scores on the last day of observation and the neuropathology scores ($p<0.0001$). This study demonstrates that the degree of peripheral nerve myelinated fiber degeneration correlates with clinical deficits in PMSF-induced potentiation of and protection against OPIDN.*


**Key Words: Organophosphorus Ester-Induced Delayed Neuropathy (OPIDN), Hen, OPIDN Promotion, PMSF, OPIDN Protection**

## INTRODUCTION

Some organophosphorus (OP) compounds have the potential to induce delayed neuropathy (OPIDN), described as a distal non-terminal degeneration of large myelinated fibers, occurring several days after a single exposure. OPIDN has been reported in different species, including humans, domestic and wild animals. The clinical signs in susceptible species (primates, cattle, sheep, water buffaloes, cats, chickens, ferrets, and turkeys) develop 6-14 days after a single exposure, and consist of incoordination, ataxia and weakness, with progression to complete flaccid paralysis within a 3 week period (Smith and Spalding, 1959; Johnson, 1975a,b; Bouldin and Cavanagh, 1979a,b; Abou-Donia, 1981; Veronesi, 1984; Padilla and Veronesi, 1985; Jortner and Ehrich, 1987; El-Fawal *et al.*, 1988, 1990; Jortner *et al.*, 1989; Stumpf *et al.*, 1989; Abou-Donia and Lapadulla, 1990;

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Lapadula *et al.*, 1992; Lotti, 1992; Pope *et al.*, 1992; Ehrich, 1996). Of these species, the domestic chicken (hen) has proven to be the most reliable animal model to study the delayed effects of organophosphate intoxications, since it readily shows clinical signs and lesions (US EPA, 1991).

OP compounds capable of inducing delayed neuropathy are known to inhibit a carboxylesterase enzyme called neurotoxic esterase (NTE) (Johnson, 1982; Aldridge, 1993; Ehrich, 1996). Determination of the percentage of brain NTE inhibition within hours (24-48 hours) of exposure of hens to OP compounds is one test required by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) before new OP insecticides can be registered for use (US EPA, 1991). It has been previously reported that delayed neuropathy can develop if more than 70-80% NTE inhibition occurs within the brain, and if the bond between OP compound and enzyme is so strong it is essentially irreversible (Johnson, 1975a,b, 1982). The OP toxicant used in the present study, phenyl saligenin phosphate (PSP), is an active congener of tri-ortho-tolyl-phosphate (TOTP) (Eto *et al.*, 1961), and is able to induce inhibition of NTE and produce delayed neurotoxicity in hens (Jortner and Ehrich, 1987; El-Fawal *et al.*, 1990).

Phenylmethylsulfonyl fluoride (PMSF), a serine/cysteine protease inhibitor, is a non-neuropathic, long acting NTE inhibitor. It can either protect against or potentiate the clinical and neuropathological effects of neuropathic organophosphate NTE inhibitors in developing or in adult animals, depending upon the sequence of PMSF and OP administration (Baker *et al.*, 1980; Pope and Padilla, 1990; Lotti *et al.*, 1991; Moretto *et al.*, 1992, 1994; Pope *et al.*, 1992, 1993; Peraica *et al.*, 1993; Funk et al., 1994; Richardson, 1995; Harp *et al.*, 1997; Randall *et al.*, 1997). One of the theories proposed concerning protection from OPIDN by pretreatment with non-neuropathic NTE inhibitors is that they shield the target site from subsequent modification by neuropathic compounds. Interestingly, while pretreatment with such non-neuropathic compounds can prevent clinical signs of OPIDN, the same compound can potentiate such clinical signs if administered after the neurotoxic OP. The mechanisms involved in OPIDN potentiation are unknown.

Neuropathological techniques such as perfusion fixation, plastic embedding, thin sectioning for high resolution light microscopy and ultrastructural examination have been used in the past to study nervous system lesions, including the characteristic changes of OPIDN (Jortner and Ehrich, 1987; El-Fawal *et al.*, 1988, 1990; Jortner *et al.*, 1989; Dyer *et al.*, 1992; Ehrich *et al.*, 1993). OPIDN is characterized by distal non-terminal axonopathy affecting larger myelinated fibers, which progress to Wallerian-type degeneration of specific ascending and descending tracts of sensorimotor pathways of the brain stem, spinal cord and peripheral nerves (Bischoff, 1967,1970; Prineas, 1969; Preissig and Abou-Donia, 1978; Bouldin and Cavanagh, 1979a,b; Krinke *et al.*, 1979; Jortner, 1982, 1984; Jortner and Ehrich 1987; Tanaka and Bursian, 1989; Lapadula *et al.*, 1992; Classen *et al.*, 1996). These neuropathologic techniques have not been used to study the morphological changes observed during promotion or protection of OPIDN, yet they would determine if changes associated with promoted OPIDN are the same as those for unpromoted OPIDN.

The objectives of this study were to critically assess PMSF-induced promotion of and protection against OPIDN in hens using neuropathological endpoints. For these studies, epoxy resin plastic-embedded tissue, high resolution light microscopy and ultrastructural examination were used. The techniques had not previously been used for study of promoted OPIDN. This study also correlates clinical signs with neuropathological findings in these modifications of OPIDN. The focus was on lesions of the hen biventer cervicis nerve, a nerve especially sensitive to functional and morphological effects of OPIDN (El-Fawal *et al.*, 1990; Dyer *et al.*, 1991). The use of resin embedding allowed thin (1 μm thick) sections which give excellent light microscopic resolution to enhance qualitative and quantitative evaluation of biventer cervicis nerve fiber degeneration. This is also the first study to examine the promotion effects of PMSF utilizing different doses of the OPIDN-inducing compound, PSP.

## METHODS

Seventy-nine adult female White Leghorn chickens (> 8 months of age) were used in the experiments described below. They were lines selected from the Cornell random-bred population obtained from the Department of Poultry Science, Virginia Polytechnic Institute and State University. They received water and a commercial poultry feed *ad libitum*, were free of apparent diseases, and vaccinated against Marek's disease.

As noted above, the delayed neurotoxicant phenyl saligenin phosphate (PSP, synthesized by Lark Enterprises, Webster MA) was employed to induce OPIDN (Jortner and Ehrich, 1987). The serine/cysteine protease inhibitor phenylmethylsulfonyl fluoride (PMSF, Sigma Chemical Company, St. Louis, MO) was used for promotion or protection from the neuropathy (Lotti *et al.*, 1991; Moretto *et al.*, 1992). The chickens were divided in 8 different groups (Table 1). To study dose related effects of PSP, single dosages of 0.5, 1.0, or 2.5 mg/kg were administered to adult hens by im injection (n = 9-10). In addition, groups of hens (n = 10) were given PMSF alone (90 mg/kg sc), PMSF four hours before 2.5 mg/kg PSP and PMSF four hours after 0.5 mg/kg or 1.0 mg/kg of PSP. For injection, PSP and PMSF were dissolved in

dimethylsulfoxide (DMSO) in concentrations such that the hens received a volume of 0.5 ml/kg (0.5 and 2.5 mg/kg PSP) or 1.0 ml/kg (1 mg/kg PSP or 90 mg/kg PMSF). The control group received 0.5 ml/kg of the DMSO vehicle sc.

During the course of the experiment, each chicken was examined daily to detect the progression of neurologic deficits, by examiners unaware of chemicals administered to the hens. Neurologic deficits were graded according to an 8 point scale previously described by Cavanagh *et al.*, 1961 (0 = normal; 8 = complete paralysis).

In order to monitor the progression of neuropathologic changes over time, biventer cervicis nerves (El-Fawal *et al.*, 1988) from 3-4 chickens in each of the categories described above were collected for light and electron microscopy, using immersion fixation (samples collected at 9 days post-dosing) or perfusion (day 15-16 post-dosing). The second procedure is time-consuming and was used when clinical signs of OPIDN were relatively stable. Immersion fixation was used at a time point when clinical signs changed daily so all samples could be collected within the same 6-hr time period. For immersion fixation, euthanasia was performed by an overdose of pentobarbital sodium administered via the cutanea ulnaris vein. The biventer cervicis nerve and muscle were then removed, straightened on a card, and immediately immersed in 3% gluteraldehyde. They were held in this fixative at 4 C for approximately 48 hours. The nerves were then dissected from the surrounding muscle and adipose tissue, and placed in a fresh 3% gluteraldehyde solution. Transcardial perfusion fixation was performed under deep general anesthesia induced by iv pentobarbital sodium, using 5% gluteraldehyde in 0.1 M phosphate buffer. After perfusion was complete, the cadavers were placed in a plastic bag, and stored at 4 C for 5 to 24 hours, to allow time for dissection of the desired tissues. The biventer muscle and attached tendon, containing approximately 3.5 cm segment of the nerve, were removed and placed in a fresh cold 5% gluteraldehyde buffered solution for 24-48 hours. Then the biventer cervicis nerves were dissected from the surrounding muscles and stored in a fresh 5% gluteraldehyde buffered solution at 4 C.

The gluteraldehyde - fixed nerves were trimmed so that cross-sections at the mid-level of the belly of the biventer cervicis muscle were examined. The nerves were post-fixed in 2% OsO4 in 0.1 M phosphate buffer, embedded in Polybed epoxy resin, sectioned at 1 μm thickness and stained with a combination of toluidine blue and safranin for light microscopy. For transmission electron microscopy evaluation, nerves in selected resin blocks were cut at 80 nm, stained with 2% uranyl acetate, Reynold's lead citrate solution (Reynolds, 1963), and evaluated for ultrastructural changes with a JEOL JEM-100CX II transmission electron microscope. A five category light microscopic neuropathologic scoring system was established, based upon percentages of degenerated fibers observed in cross sections (0: ≤ 5%; 1: > 5 and ≤ 20%; 2: > 20 and ≤ 40%; 3: > 40 and ≤ 60%; 4: > 60%), as seen in 100X color transparency photographic fields projected on a screen. Less than five percent nerve fiber degeneration was considered normal background change related to the age of the experimental subjects.

Fresh brain and cervical spinal (C1-C6 segment) cord were removed to analyze for NTE 24 hours after

**TABLE 1.** The Influence of PMSF on PSP-Induced Inhibition of Whole Brain and Spinal Cord Neuropathy Target Esterase (NTE) Activity [a,b].

| Experimental Groups | % Inhibition, brain | % Inhibition, spinal cord |
|---|---|---|
| PSP 0.5 mg/kg | 92.3 ± 0.3 | 92.3 ± 0.4 |
| PSP 1.0 mg/kg | 84.0 ± 0.2 | 92.3 ± 1.2 |
| PSP 2.5 mg/kg | 92.3 ± 0.7 | 86.0 ± 1.2 |
| PSP 0.5 mg/kg & PMSF | 95.5 ± 0.2 | 65.5 ± 2.1 |
| PSP 1.0 mg/kg & PMSF | 94.7 ± 0.2 | 98.7 ± 0.2 |
| PMSF 90 mg/kg | [c]77.0 ± 0.6 | [c]37.0 ± 2.8 |
| PMSF & PSP 2.5 mg/kg | 90.0 ± 0.3 | 82.5 ± 0.1 |

[a]PMSF (phenylmethylsulfonyl fluoride), when listed second, was given 4 hours after PSP (phenyl saligenin phosphate). When listed before PSP, it was given 12 hr prior to PSP.
[b]Mean neuropathy target esterase (NTE) inhibition ± SD, expressed as percentages. Neuropathy target esterase (NTE) activities expressed as nmol product formed/min/mg protein were 10.6 ± 1.2 for brain and 3.1 ± 1.2 for spinal cord, respectively, in vehicle-treated hens. All experimental values were significantly different from controls ($p < 0.0001$).
[c]Inhibition after PMSF 90 mg/kg was significantly less than the other groups ($p < 0.0001$; $\alpha = 0.05$).

**TABLE 2.** The Influence of PMSF on PSP-Induced Morphological Changes in Biventer Cervicis Nerves on Day 9 and Day 15 Post-Dosing[a, b].

| Experimental Groups | Lesion scores, Day 9 | Lesion scores, Day 15 |
|---|---|---|
| PSP 0.5 mg/kg | 0,0,0 | 0,0,0 |
| PSP 1.0 mg/kg | 0,0,0,1 | 2,2,2,4 |
| PSP 2.5 mg/kg | 0,0,0,1 | 3,2,3,3 |
| PSP 0.5 mg/kg & PMSF | 2,0,1,0 | 4,3,4,3 |
| PSP 1.0 mg/kg & PMSF | 1,1 | 3,3,4,4 |
| PMSF 90 mg/kg | 0,0,0,0 | 0,0,0 |
| PMSF & PSP 2.5 mg/kg | 0,0,0 | 0,0,0,1 |
| Controls | 0,0,0,0 | 0,0,0,0 |

[a]PMSF (phenylmethylsulfonyl fluoride), when listed second, was given 4 hours after PSP (phenyl saligenin phosphate). When listed before PSP, it was given 12 hr prior to PSP.
[b]Results on pathology scores are expressed according to a 0-4 grading scale.

dosing the hens. These samples were taken from all experimental groups described previously (n = 2-3). Activities of neurotoxic esterase in brain and spinal cord were determined using the method described for hens by Sprague *et al.* (1981) modified for microassay by Correll and Ehrich (1991).

Analysis of numerical data was done as follows: Means and variance for NTE activities in brain and cervical spinal cord, clinical signs, and neuropathological changes were analyzed using Duncan's multiple range test following the general linear model (GLM) statistical analysis procedure, to account for the unbalanced data between the groups. Significance of relationships between clinical signs at the time of sacrifice and lesion scores (days 9 and 15) was determined by simple linear regression (SAS/ STAT User's Guide, 1989).

## RESULTS

### Neurochemical and Clinical Studies

The degree of brain and spinal cord NTE inhibition 24 hours post - dosing is given in Table 1 for all experimental groups. The neurotoxic esterase activity was very sensitive to all doses (2.5, 1.0, or 0.5 mg/kg) of PSP alone, resulting in a very high percentage of NTE inhibition, without statistical differences among these dosages (Table 1). Both PSP and PMSF could inhibit NTE. Both inhibited NTE to the extent that any effects of the combination could not be detected.

Hens given PSP alone at 1.0 and 2.5 mg/kg or PSP plus PMSF as a promotor developed significant clinical signs (Figs. 1a and 1b). These started with mild incoordination and weakness, progressing with time to difficulty in standing upright. At time of sacrifice, severely affected birds showed marked ataxia and total inability to rise. There was a dose-effect observed with PSP alone (Fig. 1a). Administration of PMSF 90 mg/kg 4 hours following PSP dosing enhanced or promoted the clinical effect, compared to the use of PSP alone at the same level (Figs. 1a and 1b). This PMSF-induced potentiation of clinical signs was greater in hens given 1 mg/kg PSP than in hens given 0.5 mg/kg (Fig. 1b). OPIDN, as indicated by clinical signs or neuropathological examination, did not occur in control hens, hens given only PMSF, hens given PSP at 0.5 mg/kg, or hens given PMSF 12 hours prior to 2.5 mg/kg of PSP.

### Neuropathological Studies

Light microscopic evaluation of cross sections of distal regions of biventer cervicis nerves revealed a range of degenerative changes in 1.0 and 2.5 mg/kg PSP treated hens on post - dosing days 9 and 15-16, when compared to normal biventer cervicis nerves obtained from vehicle controls. As typical for OPIDN, distal axonopathy associated with Wallerian-like degeneration was the most consistent morphological change detected, and included large swollen myelinated axons with pallor of staining, intra-axonal debris and thin myelin sheaths, and collapsed axons with myelin degradation. During the Wallerian-like degeneration, myelin ovoids and axonal debris were noted in surrounding Schwann cells (Figs. 2a and 2b). More advanced lesions included endocytosis and degeneration of altered fibers by phagocytes (Fig. 2b), leading to complete replacement of degenerated myelinated fibers by columns of proliferating Schwann cells known as bands of Buengner. These changes did not differ qualitatively between the PSP 1.0 and 2.5 mg/kg groups and the PSP 0.5 or 1.0 mg/kg PMSF promoted hens (Fig. 2). Peripheral nerve lesions on days 15-16 were more extensive in promoted groups, where PMSF (90 mg/kg) was administered 4 hours after 0.5 or 1.0 mg/kg PSP challenge (Fig. 2d), compared with these levels of PSP alone (Fig. 2c). On post-dosing day 15-16, a few regenerating fibers were present in some severely affected nerves (PSP 0.5 mg/kg + PMSF 90 mg/kg; PSP 1.0 mg/kg + PMSF 90 mg/kg). By light microscopy, these appeared as small non (pre)-or thinly-myelinated neurites. The pathology scores for all groups of hens (day 9 and 15 post-dosing) are presented in Table 2. Comparison of clinical scores at the time of sacrifice and terminal peripheral nerve lesion scores gave a statistically linear relationship ($r^2$ = 0.76; p = 0.0001) (Fig. 3), therefore the pathology scores increased as the clinical signs became more severe.

As seen by transmission electron microscopy, the qualitative changes when present were similar in all groups, even though the degree of axonal injury differed (Table 2). With electron microscopic evaluation, an early stage of neuropathy in affected fibers of the biventer cervicis nerve consisted of hypertrophy and distortion of agranular-like reticulum with excess accumulation of branching cisternal membranous structures in affected axons. In addition, there was an increase in number of axonal mitochondria which subsequently underwent swelling and degeneration. As the neuropathologic changes progressed in the affected fibers, axons became swollen and contained concentrically arranged membranes, sometimes enclosing vesicles and increased numbers of mitochondria including degenerate forms, dark lamellated osmiophilic inclusions, and small electron dense granules. Other affected fibers had either rarefied and swollen, or coarse-granular and shrunken axoplasm (Fig. 4). Fragmentation of axons and myelin sheaths within Schwann cells followed, forming myelin ovoids (Fig. 4). Proliferation of the Schwann basal membrane was detected in fibers undergoing Wallerian-like degeneration. Excess collagen was sometimes visualized around degenerating fibers (Fig. 4). By electron microscopy, regenerating fibers and bands of

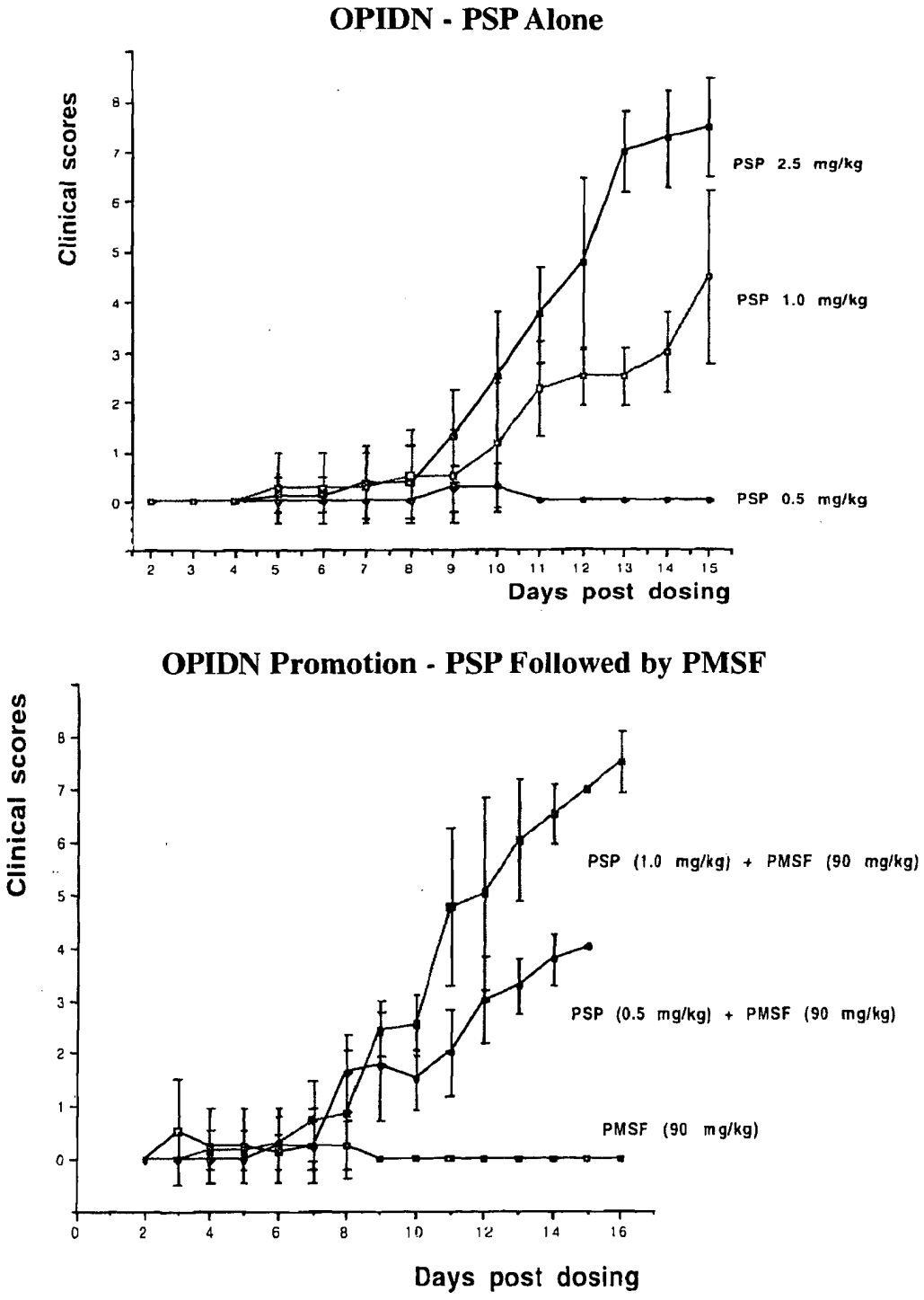


**FIG. 1.** Comparison of clinical scores (0-8) after phenyl saligenin phosphate (PSP). Fig. 1a. Dose response with 0.5 mg/kg, 1.0 mg/kg, or 2.5 mg/kg PSP. Significant differences of the mean clinical scores between PSP 1.0 mg/kg and PSP 2.5 mg/kg first occurred at day 11 post-dosing, and the terminal clinical score increased, relative to the dosage of PSP (mean ± SD). The lowest dose of PSP (0.5 mg/kg) had no discernible clinical effect (mean terminal clinical score = 0). Vehicle control hens had no clinical signs. Fig. 1b. Dose-related promotion of PSP-induced delayed neuropathy. Hens were given PSP 0.5 mg/kg or 1.0 mg/kg, followed in 4 hours by PMSF 90 mg/kg. Promotion of clinical signs seen in hens given PSP 0.5 or 1.0 mg/kg followed by administration of PMSF when compared to hens given only PSP was initially noted on day 8 post-dosing (Fig. 1a). At the end of the study, the mean clinical scores for the promoted groups (mean clinical score of promoted PSP 0.5 or 1.0 = 4.0 and 7.5 respectively; n=4) were statistically different ($p \approx 0.0001$; $\alpha = 0.05$) than when PSP 0.5 mg/kg or 1.0 mg/kg were used alone (mean clinical score PSP 0.5 or 1.0 mg/kg= 0 or 5.5; n = 4). At day 15 post-dosing, the mean clinical scores for hens given PSP 0.5 mg/kg + PMSF were significantly lower than the scores of hens given PSP 1.0 mg/kg followed by PMSF. No significant clinical effect was seen in hens dosed only with PMSF or in hens pretreated with PMSF before administration of 2.5 mg/kg PSP.

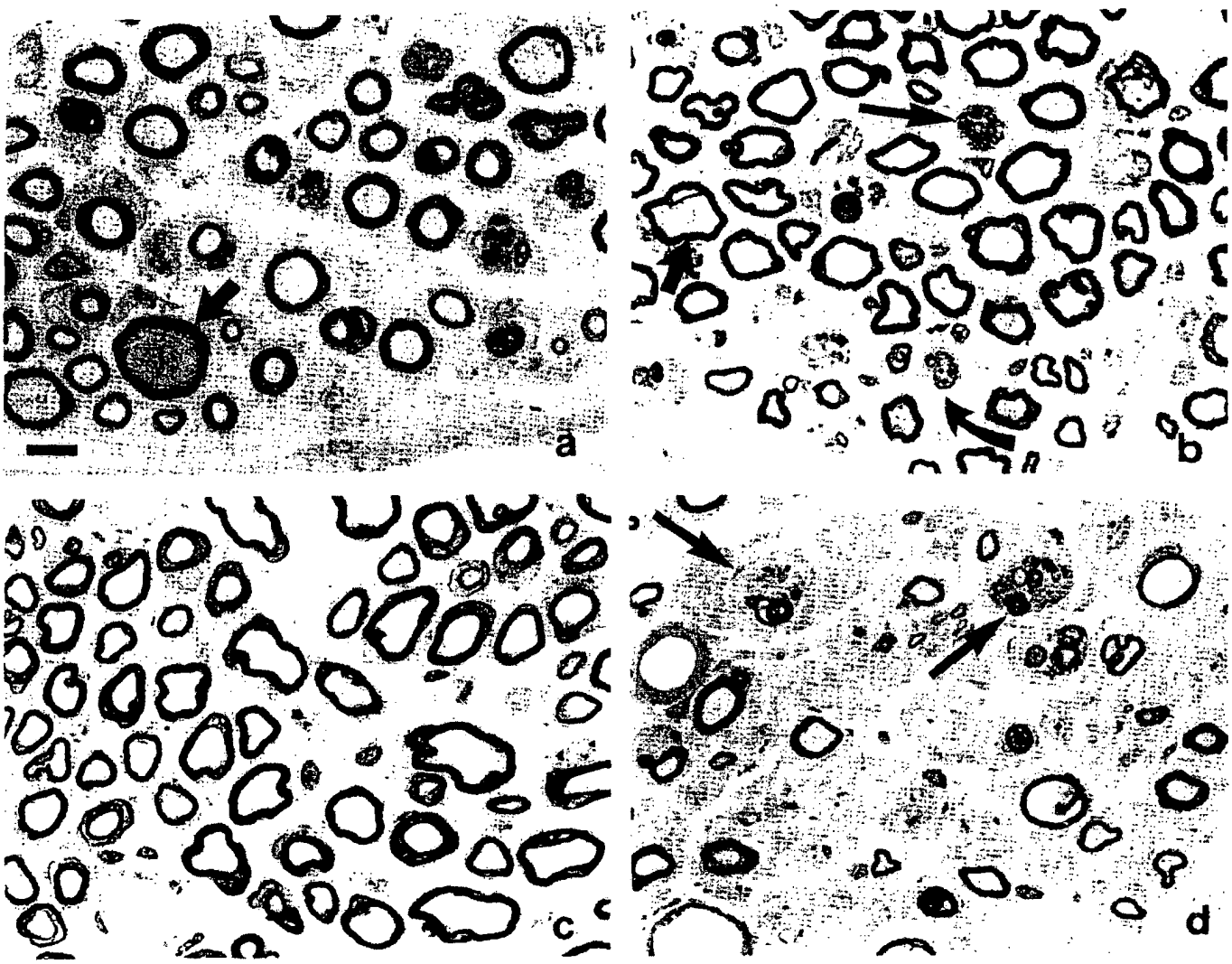


FIG. 2. Cross-soctions of the biventer cervicis nerve from hens dosed with 1.0 mg/kg PSP 9 days (Fig. 2a), or 2.5 mg/kg PSP 15 days (Fig. 2b) previously. These nerves demonstrate lesions of OPIDN such as swollen, darkly stained axons (thick arrow, Fig. 2a), pale staining swollen axons (thick arrow, Fig. 2b), profiles of myelin ovoids (thin arrow, Fig. 2b), and bands of Buengner (curved arrow, Fig. 2b). A nerve from a hen given 0.5 mg/kg PSP (not promoted) shows no significant changes at 15 days (Fig. 2c). In contrast, a biventer nerve from a promoted hen, given 0.5 mg/kg followed by 90 mg/kg PMSF, shows extensive myelinated fiber degeneration (thin arrows, Fig. 2d) and fiber loss. Only occasional, mainly small, myelinated fibers remain intact. Toluidine blue-safranin stain, bar = 10 μm.

Buengner were seen in both PSP-induced OPIDN and in promotion of that condition, with no qualitative differences among them.

## DISCUSSION

PSP, the test compound used in this study, is known for its high neuropathic potential. It can phosphorylate NTE, and the phosphorylated enzyme complex can 'age' (Johnson, 1982). In our investigation, brain NTE and spinal cord NTE were so highly sensitive to the phenyl saligenin phosphate (PSP) organophosphorus compound that a relationship between doses of PSP and percentages of enzyme inhibition could not be established. The high percentage of NTE inhibition that we observed in hens given neurotoxic doses of PSP is similar to that seen in other studies (Jortner and Ehrich, 1987; El-Fawal *et al.*, 1990). However we also noted a similar NTE inhibition with a non-neurotoxic dose (0.5 mg/kg) of PSP. In this latter group, brain NTE was inhibited at >90% by 0.5 mg/kg PSP, without development of OPIDN. This dosage of PSP when potentiated by the reversible NTE inhibitor PMSF resulted in clinical and pathological OPIDN in the absence of further NTE inhibition. The inhibition of spinal cord NTE when PMSF was added to PSP 0.5 mg/kg was less than expected, possibly due to the small number of hens analyzed (n=2). These findings,

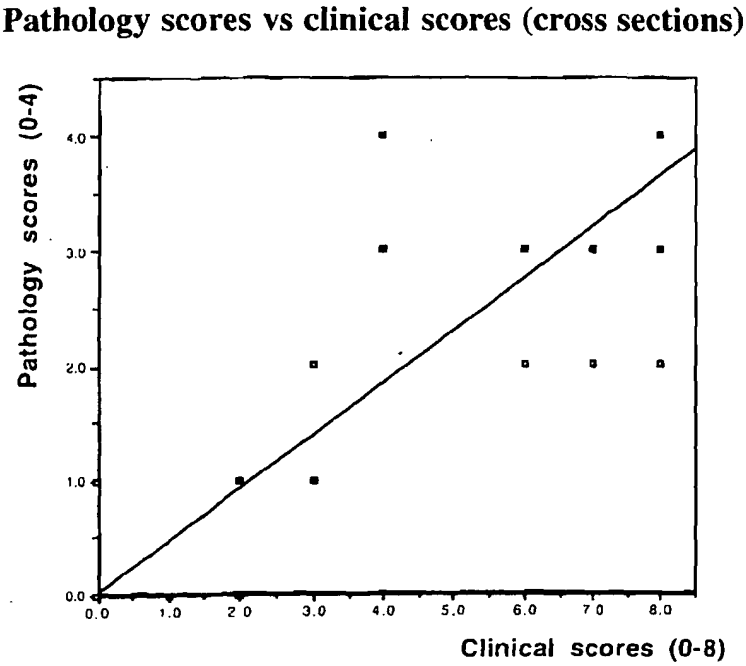


**FIG. 3.** Relationship between the clinical scores and the pathology scores in cross sections obtained at day 9 and 15. This graph represents the last clinical scores (x) obtained prior to euthanasia, and the pathology scores (y) determined in the biventer cervicis nerve. There is a significant linear relationship, determined by simple linear regression, between the last clinical scores and the pathology scores, described by the line $y = 0.0595 + 0.441x$ ($r^2 = 0.76$, $p=0.0001$).

however, suggest that inhibition of brain NTE may not be fully predictive of PSP induced delayed neuropathy, and that aging may not be related to the occurrence of the neuropathy (Lotti *et al.*, 1991; Lotti, 1992; Pope *et al.*, 1992; Johnson, 1993; Moretto *et al.*, 1994; Ehrich, 1996). Others have also suggested NTE may not be the only target responsible for initiation of OPIDN because the same reversible NTE inhibitors (PMSF) can either protect or promote OPIDN, depending upon the sequence of administration in relation to the neuropathic-inducing OP (Lotti *et al.*, 1991; Moretto *et al*, 1992; Pope *et al.*, 1992; Johnson, 1993). When preventing OPIDN, such reversible inhibitors are thought to keep neuropathy-inducing OP compounds from phosphorylating NTE. The mechanism by which these same reversible NTE inhibitors promote OPIDN is unknown. Despite this, the degree of brain NTE inhibition is recognized as the most sensitive and useful indicator of potential to develop OPIDN in OP-treated animals (Ehrich, 1996).

Until recently, all known neuropathic OP compounds were thought to undergo an aging reaction, but a more recent study suggested that this second critical step following NTE inhibition in the initiation of OPIDN may be achieved through alternative molecular processes. In support of this, Aldridge (1993) suggested that the promotion site, although other than NTE, could be similar to and/ or "linked" with that enzyme, facilitating the ability of aging near its catalytic center (Osman *et al.*, 1996). Other trophic factors are also thought to be involved in the progression of OPIDN, and could explain part of the neuropathic mechanism. These hypothesized trophic factors include ornithine decarboxylase enzymes (Pope *et al.*, 1995) and a $^3$H-DFP-binding protein within the active subunit site of NTE (Carrington and Abou-Donia, 1985; Pope *et al.*, 1992; Pope *et al.*, 1993).

This present study is unique in that it reports a dose-response statistical linear relationship between clinical signs and neuropathologic scores for OPIDN in hens sacrificed at day 9 and day 15 post-dosing, including hens protected from and hens in which the neuropathy was promoted. In this study, the relationship between scores of clinical signs and biventer cervicis nerve lesions of OPIDN ($r^2 = 0.76$) was much higher than that reported by Prentice and Roberts ($r^2 = 0.26$-$0.36$) (1983). The latter study did not include evaluation of the biventer cervicis nerve. The biventer cervicis nerve is a long peripheral nerve that is easily accessible distally, and which provides evidence of OP-induced neuropathy equivalent to that seen in the tibial nerve (Dyer *et al.*, 1991). The previous study of Dyer et al. (1991) demonstrated that axonal degeneration in the biventer cervicis nerve could be used to represent changes in more clinically relevant nervous system regions such as the tibial nerve. In the present study, the terminal clinical scores were significantly different between groups in which PSP was administered at doses of 0.5, 1.0 and 2.5

FIG. 4. Cross section of myelinated fibers in the promoted hen at 16 days. There is nerve fiber degeneration showing axonal swelling with disorganized masses of altered mitochondria, and membranous multilamellar bodies (thin arrow). An advanced stage of myelinated nerve fiber degeneration, showing fragmentation of the axon and myelin sheath within a phagocytic cell is noted (thick arrow). There is an increase in thickness of the collagen collar around affected nerve fibers (bar = 2 μm).

mg/kg, even though differences in NTE inhibition were not statistically different. Most of these PSP-dosed birds were free of clinical signs until day-9 post-dosing, emphasizing the delayed nature of this neuropathy. At the time of sacrifice, the clinical scores were elevated in hens receiving PSP at 1.0 mg/kg and 2.5 mg/kg, but absent in hens given 0.5 mg/kg, making the latter the no observed effect level (NOEL). Similar OPIDN dose-response results, including a post-dosing preclinical period, were also noted in other studies (Jortner and Ehrich, 1987; Ehrich *et al.*, 1993, 1995).

The lesions in the biventer cervicis nerve in OPIDN induced by PSP alone and in PSP neuropathy promoted by PMSF were qualitatively similar, and resembled previously reported light microscopic changes (Cavanagh, 1964; Preissig and Abou-Donia, 1978; Bouldin and Cavanagh, 1979a,b; Jortner, 1982, 1984; Jortner and Ehrich, 1987). Quantitative neuropathological changes in hens receiving 1.0 or 2.5 mg/kg of PSP were prominent, and did not significantly differ between these two groups. Thus, this was less discriminative than the clinical scores. Paralleling the clinical effects, 0.5 mg/kg did not elicit lesions.

Phenylmethylsulfonyl fluoride (90 mg/kg) administered prior to a neurotoxic dose of PSP (2.5 mg/kg) protected hens from the clinical signs and neuropathological changes of OPIDN, as has been noted in other studies with hens, rats, and cats (Baker *et al.*, 1980; Veronesi and Padilla, 1985; Pope and Padilla, 1990; Lotti *et al.*, 1991; Pope *et al.*, 1993; Randall *et al.*, 1997). PMSF's protection against OP compounds capable of inducing delayed neuropathy is thought to result from making the NTE target unavailable to neuropathic compounds. Consequently "aging" at the active site cannot occur, and thus neuropathic consequences are not observed (Pope and Padilla, 1990). In the present study, the presence of clinical signs when PSP 2.5 mg/kg was given alone and the absence of clinical signs when PMSF was given prior to PSP 2.5 mg/kg administration, supports the concept that "post-inhibition aging" of NTE is a necessary event in OPIDN (Johnson, 1982; Veronesi and Padilla, 1985). In addition, this demonstrates that a non-toxic reversible NTE inhibitor could protect susceptible species against the delayed neurotoxic effects of OPIDN, and could be a

potentially useful prophylactic agent when such an exposure is anticipated.

PMSF at 90 mg/kg administered 4 hours after PSP exposure causes quantitative promotion of morphologic changes in the biventer cervicis nerve of adult hens at least after a single exposure. Other reports support the promoting effect of PMSF on clinical signs and neuropathological changes caused by different delayed neurotoxicants in adult hens and young chicks (Pope and Padilla, 1990; Lotti *et al.*, 1991; Moretto *et al.*, 1992; Pope *et al.*, 1992; Peraica *et al.*, 1993; Osman *et al.*, 1996; Harp *et al.*, 1997; Randall *et al.*, 1997). In this work, promotion was observed following exposure to a NOEL of the organophosphate PSP in adult hens. It is difficult to establish a unifying hypothesis that would explain both protection and potentiation caused by the same PMSF compound. Alteration in the disposition of the neuropathic OP compound (Pope *et al.*, 1992), affinity for some population of nontarget esterase (Pope and Padilla, 1990), and variation in the intrinsic activities of inhibitors (partial agonists, full agonists and antagonists) (Moretto *et al.*, 1992) have all been suggested. However, potentiation is a phenomenon of environmental relevance, since chemicals with properties similar to PMSF can be concomitantly found with OP compounds, suggesting that more severe signs of OPIDN could be observed in such mixed exposures.

The present study is the first time that perfusion-fixation, and plastic (epoxy resin) embedding were used to prepare tissue to demonstrate lesions in the biventer cervicis nerve in promotion of OPIDN. This allowed us to prove that OPIDN promotion was an exaggeration of expected effects of administration of a neuropathy-inducing OP compound rather than the result of some different and additional form of axonal damage. The use of resin embedding allowed thin (1 μm thick) sections to be cut for light microscopic study, which gave excellent light microscopic resolution, superior to that in previous studies which used paraffin embedding and silver impregnation techniques (Pope *et al.*, 1992; Peraica *et al.*, 1993; Harp *et al.*, 1997; Randall *et al.*, 1997). The biventer cervicis nerve used for the present studies is especially sensitive to OPIDN (El-Fawal *et al.*, 1988, 1990), allowing both qualitative and quantitative morphological assessments. Randall *et al.* (1997) reported similar clinical and neuropathological findings, but they did not correlate clinical signs and neuropathological changes statistically. In contrast to the adult hen study of Randall *et al.* (1997), the present work also indicated promotion of a NOEL of PSP 0.5 mg/kg was possible, and therefore, showed that lesions could be induced in adult hens even after a non-toxic dose of a neuropathic OP compound. The present work is also the first study to examine neuropathological changes of promotion in OPIDN under conditions of dose-response.

This is also the first time ultrastructural changes were examined in peripheral nerve fibers of adult hens in promoted OPIDN. Ultrastructural examination proved definitively that promotion was not due to neuropathological changes other than those due to the OP compound alone. The lesions observed by transmission electron microscopy were qualitatively similar to the classical myelinated nerve fiber alterations in OPIDN (Bischoff, 1967, 1970; Prineas, 1969; Bouldin and Cavanagh, 1979b; Jortner and Ehrich, 1987).

In summary, this study assessed PMSF-induced promotion and protection of OPIDN in hens using clinical signs, NTE inhibition and neuropathologic scoring. There was a statistically significant linear relationship of $r^2 = 0.76$ between the last clinical scores (clinical score at time of sacrifice), and the neuropathological scores. Therefore, clinical signs reflect the severity of lesions observed in the biventer cervicis nerve. The disconcordance between NTE inhibition and delayed neurotoxicity, seen in this study and other studies, has caused some to question the use of NTE inhibition as a biomarker for OPIDN (Pope *et al.*, 1992; Johnson, 1993; Moretto *et al.*, 1994), although it remains the best biomarker available at this time (Ehrich, 1996). Further studies need to be conducted to better understand the early biochemical events that occur in OPIDN in order to identify more precise biomarkers of OPIDN. Investigation of mechanisms of protection and promotion of OPIDN may lead to better understanding of the pathogenetic events involved in the development of OPIDN.

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slope. **2.** A noticeable decrease: *a drop-off in attendance.*

**drop•out** (drŏp′out′) *n.* **1.a.** One who quits school. **b.** One who has withdrawn from a given social group. **2.** *Comp. Sci.* **a.** A segment of magnetic tape lacking expected information. **b.** The failure to read a bit of stored information.

**drop•per** (drŏp′ər) *n.* One that drops, esp. a small tube with a suction bulb at one end for drawing in a liquid and releasing it in drops.

**drop•ping** (drŏp′ĭng) *n.* **1.** Something dropped. **2. droppings.** The excrement of animals.

**drop shot** *n. Sports.* A shot in various racquet games in which a ball or shuttlecock drops quickly after crossing the net or hitting the wall.

**drop•sy** (drŏp′sē) *n.* Edema. No longer in scientific use. [ME *dropesie*, short for *idropesie* < OFr. *ydropisie* < Med.Lat. *ydrōpisia* < Lat. *hydrōpisis* < Gk. *hudrōpiasis* < *hudrōps*, dropsy, a dropsical person < *hudōr*, water. See **wed-**[1]*.*] — **drop′si•cal** (-sĭ-kəl) *adj.* — **drop′si•cal•ly** *adv.*

**drop•wort** (drŏp′wûrt′, -wŭrt′) *n.* A Eurasian plant *(Filipendula vulgaris)* having finely divided leaflets and small white flowers.

**dros•er•a** (drŏs′ər-ə) *n.* See **sundew.** [Gk., fem. of *droseros*, dewy < *drosos*, dew.]

**drosh•ky** (drŏsh′kē) also **dros•ky** (drŏs′-) *n., pl.* **-kies** also **-kys.** An open four-wheeled horse-drawn carriage formerly used in Russia and Poland. [Russ. *drozhki*, dim. of *drogi*, wagon, pl. of *droga*, shaft of a wagon.]

**dro•soph•i•la** (drō-sŏf′ə-lə, drə-) *n.* Any of various small fruit flies of the genus *Drosophila*, esp. *D. melanogaster* used in genetic research. [NLat. *Drosophila*, genus name : Gk. *drosos*, dew + NLat. *-phila*, pl. of *-philus*, -phile.]

**dross** (drŏs, drôs) *n.* **1.** A waste product or an impurity, esp. an oxide, formed on the surface of molten metal. **2.** Worthless, commonplace, or trivial matter. [ME *dros* < OE *drōs*, dregs.] — **dross′y** *adj.*

**drought** (drout) also **drouth** (drouth) *n.* **1.** A long period of abnormally low rainfall. **2.** A prolonged dearth or shortage. [ME < OE *drūgoth.*] — **drought′y** *adj.*

**drove**[1] (drōv) *v.* P.t. of **drive.**

**drove**[2] (drōv) *n.* **1.** A flock or herd being driven in a body. **2.a.** A large mass of people moving or acting as a body. **b.** A large body of like things. **3.a.** A stonemason's broad-edged chisel used for rough hewing. **b.** A stone surface dressed with such a chisel. [ME < OE *drāf* < *drīfan*, to drive. See **dhreibh-**[*]*.*]

**drov•er** (drō′vər) *n.* One that drives cattle or sheep.

**drown** (droun) *v.* **drowned, drown•ing, drowns.** — *tr.* **1.** To kill by submerging and suffocating in water or another liquid. **2.** To drench thoroughly or cover with or as if with a liquid. **3.** To deaden one's awareness of; blot out. **4.** To muffle or mask (a sound) by a louder sound. — *intr.* To die by suffocating in water or another liquid. [ME *drounen*, prob. of Scand. orig. See **dhreg-**[*]*.*]

**drowse** (drouz) *v.* **drowsed, drows•ing, drows•es.** — *intr.* To be half-asleep. — *tr.* **1.** To make drowsy. **2.** To pass (time) by drowsing. — *n.* The condition of being sleepy. [Perh. ult. < OE *drūsian*, to sink, be sluggish. See **dhreu-**[*]*.*]

**drows•y** (drou′zē) *adj.* **-i•er, -i•est. 1.** Dull with sleepiness; sluggish. **2.** Produced or marked by sleepiness. **3.** Inducing sleepiness. — **drows′i•ly** *adv.* — **drows′i•ness** *n.*

**dr t** *abbr.* Troy dram.

**drub** (drŭb) *v.* **drubbed, drub•bing, drubs.** — *tr.* **1.** To thrash with a stick. **2.** To instill forcefully. **3.a.** To defeat emphatically. **b.** To berate harshly. **4.** To stamp (the feet). — *intr.* **1.** To beat the ground; stamp. **2.** To pound; throb. — *n.* A blow with a heavy instrument. [Perh. Ar. *ḍaraba*, to beat.] — **drub′ber** *n.*

**drub•bing** (drŭb′ĭng) *n.* **1.** A thrashing. **2.** A total defeat.

**drudge**[1] (drŭj) *n.* A person who performs drudgery. — *intr.v.* **drudged, drudg•ing, drudg•es.** To perform drudgery. [< ME *druggen*, to labor; akin to OE *drēogan*, to work, suffer.] — **drudg′er** *n.* — **drudg′ing•ly** *adv.*

**drudge**[2] (drŭj) *n. & v. Chesapeake Bay.* Var. of **dredge**[1].

**drudg•er•y** (drŭj′ə-rē) *n., pl.* **-ies.** Tedious, menial, or unpleasant work.

**drudge•work** (drŭj′wûrk′) *n.* Drudgery.

**drug** (drŭg) *n.* **1.a.** A substance used in the diagnosis, treatment, or prevention of a disease or as a component of a medication. **b.** Such a substance as recognized or defined by the U.S. Food, Drug, and Cosmetic Act. **2.** A chemical substance, such as a narcotic, that affects the central nervous system, causing changes in behavior and often addiction. **3.** *Obsolete.* A chemical or dye. — *tr.v.* **drugged, drug•ging, drugs. 1.** To administer a drug to. **2.** To poison or mix (food or drink) with a drug. **3.** To stupefy or dull with or as if with a drug. [ME *drogge* < OFr. *drogue*, drug, perh. < MDu. *droge (vate)*, dry (cases), pl. of *drog*, dry.]

**drug•get** (drŭg′ĭt) *n.* **1.a.** A heavy felted fabric of wool or wool and cotton, used as a floor covering. **b.** A coarse rug of this fabric, made in India. **2.** A fabric woven wholly or partly of wool, formerly used for clothing. [Fr. *droguet*, prob. < *drogue*, drug, worthless object. See DRUG.]

**drug•gie** also **drug•gy** (drŭg′ē) *n., pl.* **-gies.** *Slang* takes or is addicted to drugs.

**drug•gist** (drŭg′ĭst) *n.* **1.** A pharmacist. **2.** One drugs.

**drug•gy**[1] (drŭg′ē) *Slang. adj.* **-gi•er, -gi•est.** Of or drugs or drug use.

**drug•gy**[2] (drŭg′ē) *n.* Var. of **druggie.**

**drug•store** also **drug store** (drŭg′stôr′, -stōr′) where prescriptions are filled and drugs and oth sold.

**dru•id** also **Dru•id** (drōō′ĭd) *n.* A member of priests in ancient Gaul and Britain who appear Irish legend as prophets and sorcerers. [< Lat. *dru* of Celt. orig. See **deru-**[*]*.*] — **dru•id′ic** (drōō-ĭd′ĭk) **i•cal** (-ĭ-kəl) *adj.* — **dru•id′i•cal•ly** *adv.* — **dru′i**

**drum** (drŭm) *n.* **1.** *Mus.* **a.** A percussion instrument of a hollow cylinder or hemisphere with a stretched tightly over one or both ends, played with the hands or sticks. **b.** A sound produced by ment. **2.** Something resembling a drum in shape o esp. a barrellike metal container or a metal cyli with cable, wire, or heavy rope. **3.** Any of various freshwater fishes of the family Sciaenidae that m ming sound. **4.** *Anat.* The eardrum. — *v.* **drum ming, drums.** — *intr.* **1.** To play a drum or d thump or tap rhythmically or continually. **3.** To booming reverberating sound by beating the wing birds do. — *tr.* **1.** To perform (a piece or tune) on a drum. **2.** To summon by or as if by beating a d make known to or force upon (a person) by con tion. **4.** To expel or dismiss in disgrace: *was drum the army.* — ***phrasal verb.*** **drum up. 1.** To bring continuous, persistent effort. **2.** To devise; invent *up an alibi.* [ME *drom* < MDu. *tromme*, prob. of

**drum•beat** (drŭm′bēt′) *n.* **1.** The sound produced a drum. **2.** A cause supported ardently and vehe

**drum•beat•er** (drŭm′bē′tər) *n.* One that suppor esp. vehemently. — **drum′beat′ing** *n.*

**drum•fire** (drŭm′fīr′) *n.* **1.** Heavy continuo **2.** Something likened to continuous gunfire.

**drum•head** (drŭm′hĕd′) *n.* **1.** *Mus.* The membra over the open end of a drum. **2.** *Naut.* The circu of a capstan, used to hold bars for turning.

**drum•lin** (drŭm′lĭn) *n.* An elongated hill or ridg drift. [< *drum*, ridge < Ir.Gael. *druim*, back, ri

**drum major** *n.* A man who leads a marching b corps, often twirling a baton.

**drum majorette** *n.* A woman who leads a marchi drum corps, often twirling a baton. See Usage Note

**drum memory** *n. Comp. Sci.* A memory device con rotating metal cylinder with a magnetizable coa outer surface, usu. used as random-access memo

**drum•mer** (drŭm′ər) *n. Mus.* One who plays a d

**Drum•mond•ville** (drŭm′ənd-vĭl′) A city of S Q ada, NE of Montreal. Pop. 27,374.

**drum printer** *n.* A line printer in which a revol acts as the printing element.

**drum•stick** (drŭm′stĭk′) *n.* **1.** *Mus.* A stick fo drum. **2.** The lower part of the leg of a cooked

**drunk** (drŭngk) *v.* P.part. of **drink.** — *adj.* Us **1.a.** Intoxicated with alcoholic liquor to the po ment of physical and mental faculties. **b.** Caused o by intoxication. **2.** Overcome by strong feeling *drunk with power.* — *n.* **1.** A drunkard. **2.** A bo ing.

***Usage Note:*** As an adjective the form *drunk* i icatively while the form *drunken* is now used tively: *He was drunk last night. A drunken* table beside us. The attributive use of *drunk* is acceptable in formal style. But the phrases *drunk drunk driving* are supported not only by comm also, in many jurisdictions, by a legal distinct *drunk driver* (a driver whose alcohol level exce limit) and *drunken driver* (a driver who is inc

**drunk•ard** (drŭng′kərd) *n.* One who is habitually

**drunk•en** (drŭng′kən) *adj. Usage Problem.* **1.** D or as if with strong drink; intoxicated. **2.** Hab **3.** Of, involving, or occurring during intoxicatio Note at **drunk.** — **drunk′en•ly** *adv.* — **drunk′**

**dru•pa•ceous** (drōō-pā′shəs) *adj.* **1.** Resembling or consisting of a drupe. **2.** Producing drupes.

**drupe** (drōōp) *n.* A fleshy fruit, such as a peach single hard stone that encloses a seed. [Lat. *dru* overripe olive < Gk., olive, poss. an alteration ripened on the tree : *dru-*, tree; see **deru-**[*] + ripe; see **pekʷ-**[*]*.*]

**drupe•let** (drōōp′lĭt) *n.* A small drupe, such a many subdivisions of a raspberry or blackberry

**druse** (drōōz) *n.* A crust of tiny crystals lining usu. composed of the same minerals that occur [Ger., weathered ore, prob. < MHGer. *druos*,

**druth•ers** (drŭth′ərz) *pl.n. Informal.* A choice

of generative power. **3.** In psychoanalytic theory, of or relating to the third stage of psychosexual development during which the genital organs first become the focus of sexual feeling. [Gk. *phallikos* < *phallos*, phallus. See PHALLUS.] — **phal'li•cal•ly** *adv.*

**phal•lus** (făl'əs) *n., pl.* **phal•li** (făl'ī') or **phal•lus•es.** **1.** *Anat.* **a.** The penis. **b.** The sexually undifferentiated tissue in an embryo that becomes the penis or clitoris. **2.** A representation of the penis and testes as an embodiment of generative power. **3.** The immature penis considered in psychoanalysis as the libidinal object of infantile sexuality in the male. [LLat. < Gk. *phallos*. See **bhel-2***.]

**–phane** or **–phan** *suff.* A substance resembling something specified: *tryptophan.* [< Gk. *-phanēs*, appearing < *phainesthai*, to appear. See **bhā-1***.]

**phan•er•o•gam** (făn'ər-ə-găm', fə-nâr'ə-) *n.* A plant that produces seeds. [NLat. *phanerogamus* : Gk. *phaneros*, visible (< *phainein*, to cause to appear; see **bhā-1***) + Gk. *gamos*, marriage; see -GAMOUS.] — **phan'er•o•gam'ic, phan'er•og'a•mous** (făn'ə-rŏg'ə-məs) *adj.*

**phan•tasm** (făn'tăz'əm) *n.* **1.** Something apparently seen but having no physical reality; a phantom or an apparition. **2.** An illusory mental image. **3.** In Platonic philosophy, objective reality as perceived and distorted by the five senses. [Ult. < Gk. *phantazein*, to make visible < *phantos*, visible < *phainein*, to show. See **bhā-1***.] — **phan•tas'mal** (făn-tăz'məl), **phan•tas'mic** (-tăz'mĭk) *adj.*

**phan•tas•ma** (făn-tăz'mə) *n., pl.* **-ma•ta** (-mə-tə). See **phantasm** 1, 2. [Ult. < Gk. See PHANTASM.]

**phan•tas•ma•go•ri•a** (făn-tăz'mə-gô'rē-ə, -gō'rē-) also **phan•tas•ma•go•ry** (făn-tăz'mə-gô'rē, -gō'rē) *n.* **1.a.** A fantastic sequence of haphazardly associative imagery, as seen in dreams or fever. **b.** A constantly changing scene composed of numerous elements. **2.** Fantastic imagery as represented in art. [Alteration of obsolete Fr. *phantasmagorie*, art of creating supernatural illusions : perh. *fantasme*, illusion (< OFr., ult. < Gk. *phantazein*; see PHANTASM) + *allégorie*, allegory, allegorical visual representation (< OFr., allegory < Lat. *allēgoria*; see ALLEGORY).] — **phan•tas'ma•gor'ic** (-gôr'ĭk, -gŏr'-) *adj.*

**phan•tom** also **fan•tom** (făn'təm) — *n.* **1.a.** Something apparently seen, heard, or sensed but having no physical reality; a ghost or an apparition. **b.** Something elusive or delusive. **2.** An image that appears only in the mind; an illusion. **3.** Something dreaded or despised. — *adj.* **1.** Resembling, characteristic of, or being a phantom; illusive. **2.** Fictitious; nonexistent: *phantom employees on the payroll.* [ME *fantom* < OFr. *fantosme*, prob. < VLat. **phantauma* < Gk. dial. **phantagma* < Gk. *phantasma*. See PHANTASM.]

**phantom limb pain** *n.* Pain or discomfort felt by an amputee in the area of the missing limb.

**phar.** or **Phar.** *abbr.* **1.** Pharmaceutical. **2.** Pharmacist. **3.** Pharmacopoeia. **4.** Pharmacy.

**Phar•aoh** also **phar•aoh** (fâr'ō, fā'rō) *n.* **1.** A king of ancient Egypt. **2.** A tyrant. [ME *Pharao* < LLat. *Pharaō* < Gk. < Heb. *Par'ōh* < Egypt. *pr-'o* : *pr*, house + *'o*, great.] — **Phar'a•on'ic** (fâr'ā-ŏn'ĭk) *adj.*

**pharaoh ant** *n.* A tiny yellowish-red ant *(Monomorium pharaonis)* that infests human dwellings throughout the world.

**phar•i•sa•ic** (făr'ĭ-sā'ĭk) also **phar•i•sa•i•cal** (-sā'ĭ-kəl) *adj.* **1. Pharisaic.** Of, relating to, or characteristic of the Pharisees. **2.** Hypocritically self-righteous and condemnatory. — **phar'i•sa'i•cal•ly** *adv.* — **phar'i•sa'i•cal•ness** *n.*

**phar•i•sa•ism** (făr'ĭ-sā-ĭz'əm) also **phar•i•see•ism** (-sē-ĭz'əm) *n.* **1. Pharisaism.** The doctrines and practices of the Pharisees. **2.** Hypocritical observance of the letter of religious or moral law without regard for the spirit.

**phar•i•see** (făr'ĭ-sē) *n.* **1. Pharisee.** A member of an ancient Jewish sect that emphasized strict interpretation and observance of the Mosaic law. **2.** A hypocritically self-righteous person. [ME *pharise* < OE *fariseus* and < OFr. *pharise*, both < LLat. *pharīsaeus* < Gk. *pharisaios* < Aram. *pĕrīšayyā*.]

**pharm.** or **Pharm.** *abbr.* **1.** Pharmaceutical. **2.** Pharmacist. **3.** Pharmacopoeia. **4.** Pharmacy.

**phar•ma•ceu•ti•cal** (făr'mə-sōō'tĭ-kəl) also **phar•ma•ceu•tic** (-tĭk) — *adj.* Of or relating to pharmacy or pharmacists. — *n.* A pharmaceutical product or preparation. [< LLat. *pharmaceuticus* < Gk. *pharmakeutikos* < *pharmakeutēs*, preparer of drugs, var. of *pharmakeus* < *pharmakon*, drug.] — **phar'ma•ceu'ti•cal•ly** *adv.*

**phar•ma•ceu•tics** (făr'mə-sōō'tĭks) *n.* **1.** *(used with a sing. v.)* The science of preparing and dispensing drugs. **2.** *(used with a pl. v.)* Pharmaceutical preparations; medicinal drugs.

**phar•ma•cist** (făr'mə-sĭst) *n.* One trained in pharmacy.

**pharmaco–** *pref.* Drug; medicine: *pharmacognosy.* [Gk. < *pharmakon*, poison, drug.]

**phar•ma•co•dy•nam•ics** (făr'mə-kō'dī-năm'ĭks) *n.* *(used with a sing. v.)* The study of the action or effects of drugs on living organisms. — **phar'ma•co'dy•nam'ic** *adj.* — **phar'ma•co'dy•nam'i•cal•ly** *adv.*

**phar•ma•cog•no•sy** (făr'mə-kŏg'nə-sē) *n.* The branch of pharmacology that deals with drugs in their crude or natural state. [PHARMACO- + Gk. *gnōsis*, knowledge; see GNOSIS.] — **phar'ma•cog•nos'tic** (-kŏg-nŏs'tĭk) *adj.*

**phar•ma•co•ki•net•ics** (făr'mə-kō-kĭ-nĕt'ĭks, -kī-) *n. with a sing. v.* **1.** The process by which a drug is absorbed, distributed, metabolized, and eliminated by the body. **2.** The study of this process. — **phar'ma•co•ki•net'ic** *adj.*

**phar•ma•col•o•gy** (făr'mə-kŏl'ə-jē) *n.* **1.** The science of drugs, including their composition, uses, and effects. **2.** The characteristics or properties of a drug, esp. those that make it medically effective. — **phar'ma•co•log'ic** (-kə-lŏj'ĭk), **phar'ma•co•log'i•cal** (-ĭ-kəl) *adj.* — **phar'ma•co•log'i•cal•ly** *adv.* — **phar'ma•col'o•gist** *n.*

**phar•ma•co•poe•ia** also **phar•ma•co•pe•ia** (fär'mə-kə-pē'ə) *n.* **1.** A book containing an official list of medicinal drugs together with articles on their preparation and use. **2.** A collection or stock of drugs. [NLat. < Gk. *pharmakopoios*, preparing drugs < *pharmako-*, pharmaco- + *-poios*, preparing (< *poiein*, to make; see **kʷei-2***).] — **phar'ma•co•poe'ial** (-pē'əl) *adj.*

**phar•ma•co•ther•a•py** (făr'mə-kō-thĕr'ə-pē) *n., pl.* **-pies.** Treatment of disease through the use of drugs.

**phar•ma•cy** (făr'mə-sē) *n., pl.* **-cies. 1.** The art of preparing and dispensing drugs. **2.** A place where drugs are sold; a drugstore. [Ult. < Med.Lat. *pharmacia*, a medicine < Gk. *pharmakeia*, use of drugs < *pharmakon*, drug.]

**pha•ros** (fâr'ŏs') *n.* A lighthouse. [Lat. < Gk., after the island near Alexandria, Egypt, site of an ancient lighthouse.]

**Pharr** (fär). A city of extreme S TX WNW of Brownsville. Pop. 32,921.

**Phar•sa•lus** (fär-sā'ləs) or **Phar•sa•la** (fär'sə-lə). An ancient city of Thessaly in NE Greece; site of Julius Caesar's defeat of Pompey (48 B.C.).

**pha•ryn•ge•al** (fə-rĭn'jē-əl, -jəl, făr'ĭn-jē'əl) also **pha•ryn•gal** (fə-rĭng'gəl) — *adj.* Of, relating to, located in, or extending from the pharynx. — *n. Ling.* A speech sound produced in the pharynx. [< NLat. *pharyngeus* < *pharynx*, *pharyng-*; see PHARYNX.]

**phar•yn•gi•tis** (făr'ĭn-jī'tĭs) *n.* Inflammation of the pharynx.

**pharyngo–** or **pharyng–** *pref.* Pharynx: *pharyngotomy.* [NLat. < Gk. *pharungo-* < *pharunx*, *pharung-*. See PHARYNX.]

**pha•ryn•go•scope** (fə-rĭng'gə-skōp') *n.* An instrument used in examining the pharynx. — **phar'yn•gos'co•py** (făr'ĭng-gŏs'kə-pē, făr'ĭng-) *n.*

**phar•ynx** (făr'ĭngks) *n., pl.* **pha•ryn•ges** (fə-rĭn'jēz) or **phar•ynx•es.** The section of the alimentary canal that extends from the mouth and nasal cavities to the larynx, where it joins the esophagus. [NLat. *pharynx*, *pharyng-* < Gk. *pharunx*.]

**phase** (fāz) *n.* **1.** A distinct stage of development. **2.** A temporary manner, attitude, or pattern of behavior. **3.** An aspect or part. **4.** *Astron.* One of the cyclically recurring appearances of the moon or a planet. **5.** *Phys.* **a.** A stage in a periodic process or phenomenon. **b.** The fraction of a complete cycle elapsed as measured from a reference point and commonly expressed as an angle. **6.** *Chem.* **a.** Any of the forms of matter, solid, liquid, gas, or plasma, in which matter can exist depending on temperature and pressure. **b.** A discrete homogeneous part of a material system that is separable from the rest, as ice is from water. **7.** *Biol.* A characteristic form, appearance, or stage of development that occurs in a cycle or distinguishes some individuals of a group. — *tr.v.* **phased, phas•ing, phas•es. 1.** To plan or carry out systematically in phases. **2.** To set or regulate so as to be synchronous. — ***phrasal verbs.*** **phase in.** To introduce one stage at a time. **phase out.** To bring or come to an end one stage at a time. — ***idioms.*** **in phase.** In a correlated or synchronized way. **out of phase.** In an unsynchronized or uncorrelated way. [< NLat. *phasēs*, phases of the moon < Gk. *phasis*, appearance < *phainein*, to show. See **bhā-1***.] — **pha'sic** (fā'zĭk) *adj.*

**phase contrast microscope** *n.* A microscope that uses differences in the phase of light transmitted or reflected by a specimen to form distinct, contrasting images of the specimen.

**phased array** (fāzd) *n.* An arrangement of dipoles on a antenna, in which the phase of each dipole is controlled by computer so that the beam can scan very rapidly.

**phase modulation** *n.* A type of modulation in which the of a carrier wave is varied in proportion to the amp the signal.

**–phasia** *suff.* A speech disorder of a specified kind: [Gk., speech < *phasis*, utterance < *phanai*, to say, speak; see **bhā-2***.]

**phas•mid** (făz'mĭd) *n.* Any of various insects of the Phasmida, including the leaf insects and walking sticks, common esp. in tropical areas and resembling foliage in form. [< NLat. *Phasmida*, order name < *Phasma*, type genus < Gk. *phasma*, apparition < *phainein*, to show. See **bhā-1***.]

**phat•ic** (făt'ĭk) *adj.* Of, relating to, or being speech used to share feelings or establish a mood of sociability rather than communicate information or ideas. [< Gk. *phatos*, spoken, < *phanai*, to speak. See -PHASIA.] — **phat'i•cal•ly** *adv.*

**Ph.B.** *abbr. Lat.* Philosophiae Baccalaureus (Bachelor of Philosophy).

**Ph.C.** *abbr.* Pharmaceutical Chemist.

**Ph.D.** *abbr. Lat.* Philosophiae Doctor (Doctor of Philosophy).

**pheas•ant** (fez'ənt) *n., pl.* **pheas•ants** or **pheas•ant** Various Old World birds of the family Phasianidae, having long tails and in many species brilliantly colored plumage. **2.** Any of various birds that resemble the pheasant, such as the ptarmigan. [ME *fesant* < OFr. *fesan* < Lat. *phāsiānus* < Gk. *phāsianos* (bird) of the Phasis R., pheasant < *Phasis*, river in Colchis.]

**phel•lem** (fĕl'əm, -ĕm') *n. Bot.* See **cork** 4. [Ger. *Phellem*; see **bhel-2*** + *-em* (as in *Phloëm*, phloem).]

**phel•lo•derm** (fĕl'ə-dûrm') *n.* A tissue produced by cork cambium. [Gk. *phellos*, cork; see **bhel-2*** + -DERM.]

**phel•lo•gen** (fĕl'ə-jən) *n.* See **cork cambium.** [Gk. *phellos*, cork; see **bhel-2*** + -GEN.]

**pheno–** *pref.* Var. of **pheno–**.

**phe•na•caine** (fē'nə-kān', fĕn'ə-) *n.* A white crystalline compound, $C_{18}H_{22}N_2O_2$, used in the form of its hydrochloride as a local anesthetic. [PHEN(O)- + A(CETO-) + -CAINE.]

**phe•nac•e•tin** (fə-năs'ĭ-tĭn) *n.* See **acetophenetidin.** [Alteration of component of chemical name ACETOPHENETIDIN.]

**phen•a•cite** (fĕn'ə-sīt') or **phen•a•kite** (-kīt') *n.* A beryllium silicate, $Be_2SiO_4$, occurring as vitreous crystals or grains. [Gk. *phenax*, *phenak-*, impostor + -ITE.]

**phe•nan•threne** (fə-năn'thrēn') *n.* A colorless crystalline hydrocarbon, $C_{14}H_{10}$, obtained by fractional distillation of coal tar oils and used in dyes, drugs, and explosives. [PHEN(YL) + ANTHRACENE.]

**phen•a•zine** (fĕn'ə-zēn') also **phen•a•zin** (-zĭn) *n.* A crystalline compound, $C_6H_4N_2C_6H_4$, used in making dyes. [PHEN(YL) + AZ(O)- + -INE.]

**phen•cy•cli•dine** (fĕn-sī'klĭ-dēn', -dĭn, -sĭk'lĭ-) *n.* $C_{17}H_{25}N$, used as a hallucinogen and in veterinary practice as an anesthetic; PCP. [PHEN(O)- + CYCL(O)- + -IDINE.]

**phe•net•ic** (fĭ-nĕt'ĭk) *adj.* Of, relating to, or being a classification of organisms based on overall or observable similarities rather than on phylogenetic or evolutionary relationships. [PHEN(OTYPE) + -ETIC.] — **phe•net'i•cal•ly** *adv.*

**phe•net•ics** (fĭ-nĕt'ĭks) *n. (used with a sing. v.)* The study or system of taxonomic classification.

**phenix** (fē'nĭks) *n.* Var. of **phoenix.**

**Phenix City** (fē'nĭks). A city of E AL on the Chattahoochee River across from Columbus GA. Pop. 25,312.

**pheno–** or **phen–** *pref.* **1.** Showing; displaying: *phenocryst.* **2.a.** Related to or derived from benzene: *phenol.* **b.** Related to a phenyl: *phenothiazine.* [Gk. *phaino-* < *phainein*, to show; see **bhā-1***.]

**phe•no•bar•bi•tal** (fē'nō-bär'bĭ-tôl', -tăl') *n.* A barbiturate, $C_{12}H_{12}N_2O_3$, used medicinally as a hypnotic, and an anticonvulsant.

**phe•no•bar•bi•tone** (fē'nō-bär'bĭ-tōn') *n. Chiefly Brit.* Phenobarbital.

**phe•no•cop•y** (fē'nə-kŏp'ē) *n., pl.* **-ies.** An environmentally induced, nonhereditary variation in an organism, resembling a genetically determined trait. [PHENO(TYPE) + COPY.]

**phe•no•cryst** (fē'nə-krĭst') *n.* A conspicuous, usually large crystal embedded in porphyritic igneous rock. [PHENO- + CRYST(AL).]

**phe'no•crys'tic** *adj.*

**phenol** (fē'nôl', -nōl', -nŏl') *n.* **1.** A caustic poisonous crystalline compound, $C_6H_5OH$, derived from benzene, used in resins, plastics, and pharmaceuticals. **2.** Any of a class of aromatic organic compounds having at least one hydroxyl group attached directly to the benzene ring.

**phe•no•late** (fē'nə-lāt') *n.* A salt of phenol.

**phe•nol•ic** (fĭ-nō'lĭk, -nŏl'ĭk) *adj.* Of, relating to, or derived from phenol. — *n.* Any of various synthetic resins, obtained by the reaction of phenols or aldehydes and used in molded products and coatings.

**phe•nol•o•gy** (fĭ-nŏl'ə-jē) *n.* **1.** The relationship between periodic biological phenomenon and climatic conditions. **2.** The scientific study of phenology. [PHENO(MENON) + -LOGY.]

**phe'no•log'i•cal** (fē'nə-lŏj'ĭ-kəl) *adj.*

**phe•nol•phthal•ein** (fē'nōl-thăl'ē-ĭn, -thăl'ē-ē-ĭn, -ēn') *n.* A crystalline powder, $C_{20}H_{14}O_4$, used as an acid-base indicator, in making dyes, and as a laxative. **phenol red** *n.* A red water-soluble dye, $C_{19}H_{14}O_5S$, used as an acid-base indicator and in medicine to test kidney function. **phe•nom** (fĭ-nŏm') *n. Slang.* A phenomenon, esp. a prodigy or outstanding person.

**phe•nom•e•nal** (fĭ-nŏm'ə-nəl) *adj.* **1.** Of, relating to, or being phenomena or a phenomenon. **2.** Extraordinary; astounding. **3.** *Philos.* Known or derived through the senses rather than through the mind. — **phe•nom'e•nal•ism** (fĭ-nŏm'ə-nə-lĭz'əm) *n. Philos.* The theory, set forth esp. by David Hume, that percepts are the only things present in the mind constitute the sole object of knowledge, whereas the objects of perception, their origin and cause, and the nature of the mind remain forever unknowable. — **phe•nom'e•nal•ist** *n.* — **phe•nom'e•nal•is'tic** (-nə-lĭs'tĭk) *adj.* — **phe•nom'e•nal•is'ti•cal•ly** *adv.*

**phe•nom•e•nol•o•gy** (fĭ-nŏm'ə-nŏl'ə-jē) *n. Philos.* The study of all possible appearances in human experience